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The ambiguous role of bevacizumab in progressive glioblastoma — results from the EORTC 26101 phase III trial

Since the introduction of temozolomide-based chemoradiotherapy [1], limited improvement in the treatment of glioblastoma has been made (see report on tumour-treating fields in a subsequent part of the article). Progressive glioblastoma remains a unique challenge, without any commonly recognised standard of care. Depending on an agent's availability, clinical situation, and local standards, possible therapies include: temozolomide retreatment, monotherapy with nitrosourea alkylates (such as lomustine or fotemustine), and bevacizumab monotherapy or polychemotherapy such as PCV (procarbazine, lomustine, and vincristine). However, none of these modalities demonstrated an overall survival benefit in a randomised phase 3 trial. Bevacizumab, a monoclonal antibody aimed at vascular endothelial growth factor A (VEGF-A), initially showed promising results, both as a single-agent and in combination with nitrosourea alkylates. The BELOB trial [2], a phase II study comparing bevacizumab with lomustine and with their combination, suggested superiority of the combinational approach over both single-agent arms. Additionally, the results achieved with bevacizumab alone seemed slightly inferior to lomustine monotherapy, which undermined bevacizumab's position as a single-agent modality. Recently, new data from a phase III trial shed more light on the role of bevacizumab in the treatment of progressive glioblastoma.

In the "New England Journal of Medicine" from 16 November 2017, Wick et al. [3] reported results from the EORTC 26101 trial — a randomised phase III trial comparing lomustine monotherapy (at a dose 110 mg per m^2 of body-surface area (BSA) every six weeks) with a combination therapy of lomustine (at a dose 90 mg per m^2 of BSA every six weeks, with a possible dose expansion to 110 mg in the absence of haematological adverse events) and bevacizumab (10 mg per kilogram of body weight every two weeks). Patients recruited into the trial had confirmed unequivocal progression at least three months after finishing chemoradiotherapy. The presence of isocitrate dehydrogenase (IDH) mutations and methylation of O^6-methylguanine-DNA methyltransferase (MGMT) promoter were assessed centrally. The primary end-point was overall survival. The trial recruited 437 patients, randomised in a 2:1 ratio to either combination therapy or lomustine monotherapy. The median overall survival was comparable between the arms: 9.1 months [95% confidence interval (CI) 8.1–10.1] in the combination arm and 8.6 months (95% CI 7.6–10.4) in the lomustine monotherapy arm, with a hazard ratio (HR) 0.95 (95% CI 0.74–1.21; $p = 0.65$). However, progression-free survival was significantly improved in the combination arm (4.2 months; 95% CI 3.7–4.3), compared to the monotherapy arm (1.5 months; 95% CI 1.5–2.5) — a difference that resulted in an HR of 0.49 (95% CI 0.39–0.61; $p < 0.001$). The overall response rate was 41.5% (95% CI 35.5–47.8) in patients receiving the combination therapy and 13.9% (95% CI 8.6–20.8) in patients receiving lomustine only. Any treatment-related adverse events (AEs) occurred in 63.6% and 53.1% of patients receiving, respectively, lomustine plus bevacizumab and lomustine alone. The rate of serious treatment-related AEs (grade 3–5) was considerably higher in the combination arm than in the monotherapy arm, (38.5% *vs.* 9.5%, respectively). AEs leading to death developed in 0.7% of patients (one case) receiving lomustine alone and in 1.8% of patients (five cases) receiving combination therapy. Health-related quality of life remained similar between the both arms, with the exception of a lower mean score for social functioning in the lomustine plus bevacizumab arm (81 *vs.* 66; $p = 0.001$). However, deterioration-free survival was prolonged with the combination compared to the lomustine monotherapy (12.4 *vs.* 6.7 weeks, respectively; $p < 0.001$). MGMT promoter methylation was a prognostic factor, with a longer progression-free survival and overall survival in patients with methylated MGMT promoter compared to patients with unmethylated promoter. No difference in the outcomes between experimental and control arms was seen regarding MGMT status. After the disease progression, 53% of patients in the combination arm and 65.9% in the lomustine only arm received subsequent treatment, including 35.5% of patients receiving bevacizumab after lomustine monotherapy failure.

Considering the negative results of the EORTC 26101 trial, the current role of bevacizumab in the treatment of progressive glioblastoma remains indeterminate. Despite the prolongation of progression-free

survival, the increase in response rate, and the favourable outcomes in deterioration-free survival, the combination of lomustine and bevacizumab cannot be considered as a standard-of-care for progressive glioblastoma. Lack of impact on overall survival, the most important end-point in oncology clinical trials, and the noticeable increase of serious adverse events require careful deliberation if therapy with the combination of lomustine and bevacizumab is considered. Because bevacizumab monotherapy is inferior to lomustine alone [2], possible application of bevacizumab includes the role of salvage therapy after nitrosourea derivative failure. Nitrosourea alkylates remain a valuable therapeutic option for most patients and are probably the best option from a cost-effectiveness perspective. Unfortunately, the question regarding optimal treatment schedule for progressive glioblastoma is open and awaits further studies.

Pembrolizumab improves quality-of-life outcomes compared to chemotherapy in the first-line treatment of advanced, PD-L1-positive non-small cell lung cancer: secondary results from the KEYNOTE-024 trial

The introduction of immune check-point inhibitors revolutionised treatment of several types of solid tumours, including non-small cell lung cancer (NSCLC). Both PD-1 and PD-L1 inhibitors show activity in the second-line treatment of both squamous and non-squamous NSCLC. Recently, pembrolizumab, a monoclonal antibody targeting PD-1, showed superior outcomes in progression-free and overall survival when compared with a standard-of-care platinum-based chemotherapy in patients with a PD-L1 present on at least 50% of tumour cells (KEYNOTE-024 trial [4]). The difference in overall survival between pembrolizumab and chemotherapy remained significant despite a high rate of a post-progression cross-over. Additionally, pembrolizumab resulted in lower rates of treatment-related adverse events, with a nearly 50% reduction of grade 3–5 treatment-related AEs. The question of whether improved efficacy and a favourable toxicity profile resulted in an improvement of quality-of-life was recently answered.

Brahmer et al. [5] reported quality-of-life assessment from the KEYNOTE-024 trial on 9 November 2017 in The Lancet Oncology. The study compared pembrolizumab with a platinum-based chemotherapy in over 300 patients with treatment-naïve, locally advanced or metastatic lung cancer (154 patients in the pembrolizumab arm and 151 patients in the chemotherapy arm). The quality-of-life analysis included patient-reported outcomes (PROs) obtained at day 1 of the first three cycles, every nine weeks afterwards, and at treatment discontinuation. Quality-of-life was assessed with: the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 Items (QLQ-C30); the EORTC Quality of Life Questionnaire Lung Cancer 13 items (QLQ-LC13); and the European Quality of Life 5 Dimensions — 3 Level (EQ-5D-3L) questionnaire. Two key end-points were evaluated: the baseline-to-week-15 change in the QLQ-C30 global health status/quality-of-life (QHS/QOL) score and the time to deterioration of composite of cough, chest pain, and dyspnoea assessed in the QLQ-LC13. Most of the patients included in the study completed all three questionnaires at the treatment initiation, with a satisfying compliance rated at week 15 of about 80%. Most of the data missing were due to death, adverse events, and disease progression. Results regarding baseline-to-week-15 change in QLQ-30 QHS/QOL domain significantly favoured the pembrolizumab arm, with an improvement from baseline of 6.9 (95% CI 3.3-10.6) points and a decrease of 0.9 (95% CI 4.8–3.0) points in patients receiving, respectively, pembrolizumab and chemotherapy. This resulted in a difference in least-squares means of 7.8 points (95% CI 2.9–12.8; two-sided nominal $p = 0.002$). Similarly, the time to deterioration in a composite of cough, chest pain, and dyspnoea in the QLQ-LC13 was significantly better for immunotherapy — median not reached (95% CI 8.5–not reached) in the pembrolizumab arm *vs.* 5.0 months (95% CI 3.6–not reached) in the chemotherapy arm (HR of 0.66; 95% CI 0.44–0.97; two-sided nominal $p = 0.029$). Additionally, nearly all other quality-of-life domains showed better results in the pembrolizumab arm, although most of them remained only numerically superior.

Combined with the efficacy results published previously [4], the presented data strongly support adoption of pembrolizumab as the standard-of-care in the first-line treatment of advanced or metastatic NSCLC with a PD-L1 expression of at least 50%. Even clear benefit in overall survival remains disappointing if associated with a decrease in the quality of life. From this perspective, immunotherapy offers a significant benefit over both chemotherapy and, in cases such as renal cell carcinoma, targeted therapy. However, stunning costs of immunotherapy might be comprehended as a financial toxicity, and one, unfortunately, undetectable in the quality-of-life assessment.

Results from randomised phase III IMvigor221 study — a tie between chemotherapy and immunotherapy in the treatment of platinum-resistant, advanced urothelial carcinoma

Despite limited advancements in the treatment of metastatic urothelial carcinoma during the last two decades, recent introduction of immune check-point inhibitors brought deep changes to the field. Currently, several PD-1 and PD-L1 inhibitors have been approved either by the Food and Drug Administration (FDA) in the USA or by European Medicines Agency (EMA) in the European Union for the treatment of urothelial carcinoma. Immunotherapy can now be considered a standard-of-care in first-line treatment for platinum-ineligible patients or in second- and subsequent-line treatment after failure of platinum-based chemotherapy. However, only one compound, pembrolizumab, showed an improvement of overall survival in the phase III trial in platinum-refractory patients [6]. Novel phase III trial data regarding PD-L1 inhibition in this population were recently published, with results somehow dissonant with previous reports.

Results from the IMvigor221 trial were published on 18 December 2017 in The Lancet Oncology by Powles et al. [7]. IMvigor221 was a phase III, open-label, randomised controlled trial in patients with urothelial carcinoma progressing after a platinum-based chemotherapy. It compared atezolizumab, a PD-L1 inhibitor given at a dose of 1200 mg every three weeks, with a physician's choice of chemotherapy (either vinflunine, paclitaxel, or docetaxel). The primary end-point was overall survival, with a comparison between both arms statistically tested in a hierarchical fixed-sequence: firstly, in the patients with PD-L1 expression on over 5% of tumour-infiltrating immune cells (IC 2/3 group), then in patients with PD-L1 expression of over 1% (IC 1/2/3 group) and then in an intention-to-treat population (ITT). A lack of a statistically significant difference in overall survival at each step excluded further analysis. The study recruited 931 patients, randomised in a 1:1 ratio to both of the arms. About 2/3 of patients received at least one previous line of chemotherapy in a metastatic setting, and the other 1/3 progressed within 12 months after adjuvant platinum-based chemotherapy. In the primary analysis of overall survival in the IC2/3 population, no significant difference between both arms was seen [11.1 months (95% CI 8.6–15.5) for atezolizumab *vs*. 10.6 months (95% CI 8.4–12.2) for chemotherapy, with an HR of 0.87 (95% CI 0.63–1.21; p = 0.41)]. Objective response rate in the IC2/3 population was 23% (95% CI 15.6–31.9) and 21.6% (95% CI 14.5–30.2) for atezolizumab and chemotherapy, respectively. Duration of response was numerically improved with atezolizumab in IC2/3 patients [15.9 months (95% CI 10.4–not reached) *vs*. 8.3 months (95% CI 5.6–13.2)]. Negative results from the IC2/3 population precluded further formal analyses in IC1/2/3 and ITT populations. However, exploratory analysis in the ITT population showed marginally significant improvement in overall survival: 8.6 months (95% CI 7.8–9.6) in the atezolizumab group and 8.0 months (95% CI 7.2–8.6) in the chemotherapy group, with a stratified HR of 0.85 (95% CI 0.73–0.99). Additional biomarker analysis showed improved overall survival with atezolizumab in patients with high (at or above median) tumour mutational burden (11.3 months (95% CI 8.7–13.2) *vs.* 8.3 months (95% CI 7.2–10.4), with a HR of 0.68 (95% CI 0.51–0.90), in contrast to similar overall survival between arms in patients with low (below median) tumour mutational burden [8.3 months (95% CI 6.4–9.8] for atezolizumab *vs*. 8.1 months (95% CI 6.2–10.4) for chemotherapy and a HR of 1.00 (95% CI 0.75–1.32)]. The benefit of atezolizumab was even more evident in patients with a high tumour mutational burden and the presence of IC 2/3. Rates of treatment-related adverse events of any grade and grade 3–4 were lower in the atezolizumab arm compared than in the chemotherapy arm. No new or unexpected immune-related adverse events were seen. Most of the quality-of-life domains were numerically better in the atezolizumab group, although median time to deterioration was similar between both arms.

Negative results from the presented IMvigor221 study are contrary to the positive outcomes of the KEYNOTE-045 study [6], both undertaken in comparable populations. The question of why one immune check-point inhibitor trial shows a statistically significant improvement in overall survival and other does not challenges our current understanding of cancer immunotherapy. Whether this arises from varying trial design, disparities between patient characteristics, heterogeneity of PD-1/PD-L1 testing, or differences between check-point inhibitor activity, remains an unknown. However, with a wider utilisation of PD-1 and PD-L1 inhibitors, most of the novel studies are vulnerable to the influence of a post-trial check-point inhibitor exposure. This may comprise a significant interference to overall survival analyses, hindering the understanding of conflicting results. Nevertheless, the effectiveness of check-point inhibitors in the treatment of platinum-resistant advanced urothelial carcinoma is unquestionable and check-point inhibitors may be considered as a standard of care in this setting.

Tumour-treating fields — a novel modality in the treatment of newly diagnosed glioblastoma.

As mentioned previously, the last decade brought little to no improvement in the treatment of glioblastoma. Surgical debulking, whenever possible, followed by a concomitant radiochemotherapy with temozolomide maintenance have remained the standard of care since 2005 [1]. Several novel therapeutic approaches, such as inhibition of angiogenesis or immunotherapy with peptide vaccines, failed to improve overall survival, either as part of initial therapy or as a salvage treatment. However, in 2015 an initial report on the effectiveness of a novel modality — tumour-treating fields (TTFs) — raised a great deal of interest because a pre-planned interim analysis showed improved progression-free and overall survival [8]. TTFs are altering electric fields, delivered at intermediate-frequency (200 kHz) via transducer arrays attached to the scalp. The generated fields disturb the action of karyokinetic spindle and interrupt cell division, contributing to the induction of apoptosis. Lately, novel results have confirmed TTFs efficacy in glioblastoma treatment.

In the issue of JAMA from 19 December 2017, Stupp et al. [9] published final results from a randomised phase III trial comparing TTFs with temozolomide maintenance with temozolomide alone in patients with glioblastoma, who completed concomitant radiotherapy after tumour resection or biopsy. The TTFs were administered for at least 18 hours per day, along with a standard temozolomide at a dose of 150–200 mg/m^2 for five days in 28-day cycles. If applicable, the therapy comprised of 6–12 chemotherapy cycles, depending on local standards. Additionally, TTFs could have been maintained until second radiological progression or maximally for 24 months. The primary end-point was progression-free survival and the secondary end-point was overall survival. The study recruited 695 patients, randomised in a 2:1 ratio to either TTFs plus temozolomide or temozolomide alone. After a median follow-up of 40 months, the primary end-point was met. The median progression-free survival was 6.7 months (95% CI 6.1–8.1) in the TTF arm and 4.0 months (95% CI 3.8–4.4) months in temozolomide alone arm, with an HR of 0.63 (95% CI 0.52–0.76; $p < 0.001$). Patients receiving TTFs also had better overall survival, with a median of 20.9 months (95% CI 19.3–22.7) *vs.* 16.0 months (95% CI 14.0–18.4) for the TTF arm and standard arm, respectively. This difference was statistically significant, with an HR of 0.63 (95% CI 0.53–0.76; $p < 0.001$). Five-year survival rates were 13% (95% CI 9–18) in patients receiving TTFs and 5% (95% CI 2–11) in patients receiving temozolomide only ($p < 0.001$). The positive impact of TTFs on progression-free survival and overall survival remained significant in all subgroups analysed, including patients with methylated and unmethylated MGMT promoter region. Rates of adverse events were similar between both arms, especially when considering longer time of treatment in the TTFs plus temozolomide arm. An adverse event unique to TTFs application — skin irritation — was mild to modest in most of the cases, with only 2% of patients developing grade 3 skin reaction. Quality-of-life analysis also showed better results with TTFs plus temozolomide compared to temozolomide alone. This included prolonged time to a six-point decline in the Mini-Mental State Examination score and to a 10-point decrease in Karnofsky performance status.

The presented study is the first randomised phase 3 trial in a decade to show statistically significant improvement of overall survival in patients with glioblastoma. TTFs represent a novel modality in glioblastoma treatment and a valuable addition to the current armamentarium. Several ongoing trials are evaluating the effectiveness of TTFs in solid tumours other than glioblastoma, with some intriguing preliminary results seen in pancreatic cancer. Unfortunately, common application of a sophisticated equipment such as TTFs outside a clinical trial might be challenging. Currently, a combination of TTFs and temozolomide should be considered the standard maintenance therapy after a completed chemoradiotherapy, at least until the next "breakthrough" trial — hopefully in less than another decade.

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